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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/599,974	02/14/1996	JEFFREY M. FRIEDMAN	600-1-162CP1	1513

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DAVID A JACKSON
KLAUBER AND JACKSON
411 HACKENSACK AVENUE
HACKENSACK, NJ 07601

EXAMINER	
O HARA, EILEEN B	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 07/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/599,974	FRIEDMAN ET AL.	
	Examiner	Art Unit	
	Eileen O'Hara	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21,24,26-28,34-48,51,52 and 67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *28* is/are allowed.

6)☒ Claim(s) *21,24,26,27,34-48,51,52 and 67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 January 1997* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

S.O.O

DETAILED ACTION

1. Claims 21, 24, 26-28, 34-48, 51, 52 and 67 are pending in the instant application. Claims 24, 27 and 67 have been amended and claim 22 has been canceled as requested by Applicant in the Paper filed May 6, 2005.

All claims are currently under examination.

Withdrawn Objections and Rejections

2. Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

New Rejections or Objections

Specification

3. The disclosure is objected to because of the following informalities: on pages 78-79, text is missing.

Appropriate correction is required. Applicants are advised about the possibility of adding new matter to the specification.

Claim Objections

4. Claims 39-42, 43, 44, 47 and 48 are objected to because of the following informalities:

4.1 Claims 39-43 are objected to because "**An** unicellular host" should be "**A** unicellular host" to be grammatically correct.

4.2 Claims 43 and 44 are objected to because they encompass a host cell that is a bacteria, wherein the host cell is in tissue culture, and bacteria are not grown in tissue culture.

4.3 Claims 47 and 48 are objected to because they recite "culturing a cell according to **any** claim 43" or recite "culturing a cell according to **any** claim 44" which is not grammatically correct. Deletion of the word "any" would overcome the rejection.

4.4 Claim 26 objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The DNA molecule of SEQ ID NO: 9 is murine.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 27, 36, 38, 40, 42, 44, 46, 48, 52 and 67 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 27, 36, 38, 40, 42, 44, 46, 48, 52 and 67 are indefinite because they recite "consisting essentially of amino acids 28-805 of SEQ ID NO: 10, and the phrase "consisting essentially of" refers to compositions, so it is not clear how it pertains to a protein.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6.1 Claims 24, 26, 27, 34-48, 51 and 52 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated DNA molecule encoding on expression a soluble leptin receptor which is a DNA molecule of SEQ ID NO: 9, it does not reasonably provide enablement for an isolated DNA molecule encoding on expression a soluble leptin receptor which is the complement of SEQ ID NO: 9. The instant specification on teaches that the nucleic acid sequence of SEQ ID NO: 9 encodes the leptin receptor of SEQ ID NO: 10. However, claim 24 in the preamble recites:

"An isolated DNA molecule encoding on expression a soluble leptin receptor polypeptide selected from the group consisting of:

a. a DNA molecule of SEQ ID NO: 9;

b. a DNA molecule complementary to the DNA molecule defined in (a);"

However, the complement of SEQ ID NO: 9 would not encode the leptin receptor. Part (c) of claim 24 also encompasses a DNA that encodes a leptin receptor encoded by the complement of the encoding nucleic acid.

6.2 Claims 51 and 52 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an expression vector comprising DNA encoding a leptin receptor, does not reasonably provide enablement for transgenic vector comprising DNA encoding a leptin receptor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention

commensurate in scope with these claims. Claims 51 and 52 are drawn to transgenic vectors comprising DNA encoding leptin receptor. The specification at page 13, lines 18-21 and pages 78-80, teaches that a transgenic vector may be a viral vector or naked DNA for administration to a subject for gene therapy, and therefore the claims encompass gene therapy. The specification also asserts that the claimed gene products can be expressed in transgenic animals and any technique known in the art may be used to introduce a transgene into animals to produce the founder lines of transgenic animals (pg 21, line 27 to pg 23, line 3), and therefore the claims encompass transgenic animals.

The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The claims are directed to a broad genus of transgenic vector which comprises the claimed DNA. The specification contemplates three subgenera in which vectors can be made and used. Specifically, the specification contemplates making and using the vectors in host cells in culture to produce the encoded leptin receptor, in gene therapy, and in multicellular, transgenic organisms.

Case law directs that the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim non-enabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be

inoperative or operative with expenditure of no more than is normally required in the art. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984) (prophetic examples do not make the disclosure nonenabling). However, claims reading on significant numbers of inoperative embodiments would render claims non-enabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative. *Ibid.*; *In re Cook*, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971). Since the instant specification asserts that the claimed host cells can be made and used in three contexts, two of which are not enabled for the reasons set forth below, the instant fact pattern corresponds to the second situation wherein the claims encompass a significant number of inoperative embodiments and thus should be rejected under 35 U.S.C. § 112, first paragraph, as not being enabled for the full scope of the claims.

The specification asserts that host cells comprising vectors can be made and used in three contexts. 1) The specification contemplates making and using isolated host cells in culture to produce the encoded protein recombinantly. Such is enabled, since the specification and prior art provide specific guidance on how to make and use host cells comprising expression vectors for this purpose. Undue experimentation would not have been required of the skilled artisan to make and use the claimed vectors in this context.

2) The specification also asserts that the claimed gene products can be expressed in transgenic animals and any technique known in the art may be used to introduce a transgene into animals to produce the founder lines of transgenic animals (pg 21, line 27 to pg 23, line 3). However, there are no methods or working examples disclosed in the instant application whereby a multicellular animal with the incorporated claimed gene is demonstrated to express the

encoded peptide. The unpredictability of the art is *very high* with regards to making transgenic animals. For example, Wang et al. (Nuc. Acids Res. 27: 4609-4618, 1999; pg 4617) surveyed gene expression in transgenic animals and found in each experimental animal with a single "knock-in" gene, multiple changes in genes and protein products, often many of which were unrelated to the original gene. Likewise, Kaufman et al (Blood 94: 3178-3184, 1999) found transgene expression levels in their transfected animals varied from "full" (9 %) to "intermediate" to "none" due to factors such as "vector poisoning" and spontaneous structural rearrangements (pg 3180, col 1, 2nd full paragraph; pg 3182-3183). Additionally, for example, the specification discloses that two possible techniques used to introduce the claimed transgene into animals include pronuclear microinjection and gene targeting in embryonic stem cells. However, the literature teaches that the production of transgenic animals by microinjection of embryos suffers from a number of limitations, such as the extremely low frequency of integration events and the random integration of the transgene into the genome which may disrupt or interfere with critical endogenous gene expression (Wigley et al. Reprod Fert Dev 6: 585-588, 1994). The inclusion of sequences that allow for homologous recombination between the transgenic vector and the host cell's genome does not overcome these problems, as homologous recombination events are even more rare than random events. Therefore, in view of the extremely low frequency of both targeted and non-targeted homologous recombination events in microinjected embryos, it would have required undue experimentation for the skilled artisan to have made any and all transgenic non-human animals according to the instant invention. Furthermore, regarding gene targeting in embryonic stem cells, the specification does not provide guidance for identifying and isolating embryonic stem cells or for identifying other

embryonal cells which are capable of contributing to the germline of any animal. At the time of filing, Campbell et al. teaches that, "in species other than the mouse the isolation of ES cells has proved more difficult. There are reports of ES-like cell lines in a number of species...However, as yet there are not reports of any cell lines which contribute to the germ line in any species other than mouse" (Campbell et al. Theriology 47(1): 63-72, 1997; see pg 65, 2nd paragraph). Thus, based on the art recognized unpredictability of isolating and using embryonic stem cells or other embryonal cells from animals other than mice to produce transgenic animals, and in view of the lack of guidance provided by the specification for identifying and isolating embryonal cells which can contribute to the germ line of any non-human mammal other than the mouse, such as dogs or cows, the skilled artisan would not have had a reasonable expectation of success in generating any and all non-human transgenic animals using ES cell technology.

3) The specification also discloses that nucleotide constructs comprising the claimed gene can be used to genetically engineer host cells to express such products in vivo and that these products can be used in gene therapy approaches (pg 13, lines 18-21). However, the specification does not teach any methods or working examples that indicate the claimed nucleic acid is introduced and expressed in a cell for therapeutic purposes. The disclosure in the specification is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. For example, the specification does not teach what type of vector would introduce the claimed nucleic acid into the cell or in what quantity and duration. Relevant literature teaches that since 1990, about 3500 patients have been treated via gene therapy and although some evidence of gene transfer has been seen, it has generally been inadequate for a meaningful clinical response (Phillips, A., J Pharm Pharmacology 53: 1169-1174, 2001;

abstract). Additionally, the major challenge to gene therapy is to deliver DNA to the target tissues and to transport it to the cell nucleus to enable the required protein to be expressed (Phillips, A.; pg 1170, ¶ 1). Phillips also states that the problem with gene therapy is two-fold: 1) a system must designed to deliver DNA to a specific target and to prevent degradation within the body, and 2) an expression system must be built into the DNA construct to allow the target cell to express the protein at therapeutic levels for the desired length of time (pg 1170, ¶ 1). Therefore, undue experimentation would be required of the skilled artisan to introduce and express the claimed vector into the cell of an organism to treat disease. Additionally, gene therapy is unpredictable and complex wherein one skilled in the art may not necessarily be able to introduce and express the claimed nucleic acid in the cell of an organism or be able to produce the encoded protein in that cell.

Due to the large quantity of experimentation necessary to generate a transgenic animal expressing the disclosed protein and to introduce and express the claimed nucleic acid in a cell of an organism for therapy, the lack of direction/guidance presented in the specification regarding how to introduce the claimed nucleic acid in the cell of an organism to be able produce the encoded protein, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of making transgenic animals and the unpredictability of transferring genes into an organism's cells, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Maintained Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 21, 27, 34-48, 51, 52 and 67 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants traverse the rejection on page 8 of the response, and submit that the claims, particularly as amended and presented herein, contain subject matter which was described in the specification in such a way as to convey to the skilled artisan that the inventors had possession at the time of filing. Applicants submit that each and any of the nucleic acids claimed in the instant Application meets the written description requirement, having a precise definitive as to structure or formula, particularly herein as to nucleic acid sequence.

Applicants' arguments have been fully considered but are not deemed persuasive. Claims 21, 27 and 67 each encompass a specific nucleic acid sequence encoding a specific polypeptide, *or allelic variants thereof*, which would not have the same sequences. No allelic variants are disclosed in the specification.

Therefore, the rejection is maintained.

It is believed that all pertinent arguments have been answered.

Conclusion

8.1 Claim 28 is allowed.

8.2 Claims 21, 24, 26, 27, 34-48, 51, 52 and 67 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (571) 272-0878. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached at (571) 272-0829.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://portal.uspto.gov/external/portal/pair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Eileen B. O'Hara

Eileen B. O'Hara, Ph.D.

Patent Examiner

EILEEN B. O'HARA
PATENT EXAMINER